Heliyon 10 (2024) e34636

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

# Curcumin-loaded soluplus® based ternary solid dispersions with enhanced solubility, dissolution and antibacterial, antioxidant, anti-inflammatory activities

Memoona Ishtiaq [a], Hina Manzoor [b], Ikram Ullah Khan [a], Sajid Asghar [a], Muhammad Irfan [a,c], Norah A. Albekairi [d], Abdulrahman Alshammari [d], Abdulrahman F. Alqahtani [e], Saad Alotaibi [e], Rabia Munir [a], Pervaiz A. Shah [f], Liaqat Hussain [g], Muhammad Abubakar Saleem [a,h], Fizza Abdul Razzaq [a], Syed Haroon Khalid [a,i,*]

[a] *Department of Pharmaceutics, Faculty of Pharmaceutical Sciences, Government College University, Faisalabad 38000, Pakistan*
[b] *Faculty of Pharmaceutical Sciences, Government College University, Faisalabad 38000, Pakistan*
[c] *College of Pharmacy, Freie Universitaet Berlin, Germany*
[d] *Department of Pharmacology and Toxicology, College of Pharmacy, King Saud University, Post Box 2455, Riyadh, 11451, Saudi Arabia*
[e] *Department of Pharmacy, Riyadh Security Forces Hospital, Ministry of Interior, Kingdom of Saudi Arabia*
[f] *University College of Pharmacy, University of the Punjab, Lahore, 54590, Pakistan*
[g] *Department of Pharmacology, Faculty of Pharmaceutical Sciences, Government College University Faisalabad, Faisalabad 38000, Pakistan*
[h] *Unison Chemical Works, Post Office Araian 15 Km Raiwind Road, Lahore, Pakistan*
[i] *Faculty of Pharmacy, Universiti Teknologi MARA (UiTM), Cawangan Selangor, Kampus Puncak Alam, 42300 Bandar Puncak Alam, Selangor, Malaysia*

ARTICLE INFO

*Keywords:*
Curcumin
Poloxamer
Anti-inflammatory agents
Solubility
Polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer
Solid dispersions
Antibacterial
Antioxidants

ABSTRACT

Amorphous solid dispersion (ASD) has emerged to be an outstanding strategy among multiple options available for improving solubility and consequently biological activity. Interestingly several binary SD systems continue to exhibit insufficient solubility over time. Therefore, the goal of current research was to design ternary amorphous solid dispersions (ASDs) of hydrophobic model drug curcumin (CUR) to enhance the solubility and dissolution rate in turn, presenting enhanced anti-bacterial, antioxidant and anti-inflammatory activity. For this purpose several ternary solid dispersions (TSDs) consisting of Soluplus®, Syloid® XDP 3150, Syloid® 244 and Poloxamer® 188 in combination with HPMC E5 (binary carrier) were prepared using solvent evaporation method. Both solubility and dissolution testing of prepared solid dispersion were performed to determine the increase in solubility and dissolution. Solid state investigation was carried out utilizing infrared spectroscopy, also known as Fourier transform infrared spectroscopy (FTIR), scanning electron microscopy (SEM),Differential scanning calorimetry (DSC) and X-ray diffraction (XRD).Optimized formulations were also tested for their biological effectiveness including anti-bacterial, anti-oxidant and anti-inflammatory activity. Amid all Ternary formulations F3 entailing 20 % soluplus® remarkably improved the solubility (186 μg/ml ± 3.95) and consequently dissolution (91 % ± 3.89 %) of curcumin by 3100 and 9 fold respectively. These

* Corresponding author. Department of Pharmaceutics, Faculty of Pharmaceutical Sciences, Government College University, Faisalabad 38000, Pakistan.
*E-mail addresses:* syedharoonkhalid@gcuf.edu.pk, haroonkhalid80@gmail.com, haroonkhalid@uitm.edu.my (S.H. Khalid).

https://doi.org/10.1016/j.heliyon.2024.e34636
Received 16 December 2023; Received in revised form 11 July 2024; Accepted 12 July 2024
Available online 14 July 2024

finding were also supported by FTIR, SEM, XRD and DSC. In-vitro antibacterial investigation of F3 also demonstrated significant improvement in antibacterial activity against both gram positive (*Staphylococcus aureus, Bacillus cereus)* and gram negative (*Pseudomonas aeruginosa*, *Escherichia coli)* bacteria. Among all the tested strains *Staphylococcus aureus* was found to be most susceptible with a zone of inhibition of 24 mm ± 2.87. Antioxidant activity of F3 was also notably enhanced (93 % ± 5.30) in contrast to CUR (69 % ± 4.79). In vitro anti-inflammatory assessment also exhibited that F3 markedly protected BSA (bovine serum albumin) from denaturation with percent BSA inhibition of 80 % ± 3.16 in comparison to CUR (49 % ± 2.91). Hence, F3 could be an effective solid dispersion system for the delivery of model hydrophobic drug curcumin.

## 1. Introduction

Curcumin constitutes as one of the principal functioning components of turmeric, a spice which is obtained from the root of plant *Curcuma longa*. This plant belongs to ginger family that grows widely in Southeast Asia [1]. It is commonly used as a food coloring additive in different cuisines around the world however lately it has gained an excessive amount of attention for its wide range of medicinal qualities particularly anti-oxidant, anti-microbial and anti-inflammatory effects [2]. Structurally, Curcumin features two polar phenyl rings coupled with two hydroxyl and *ortho*-methoxy groups. These polar phenyl rings are axially joined by an aliphatic chain (C7) which makes curcumin essentially insoluble in water. This lack of solubility in water together with poor oral bioavailability has hindered its clinical applications [3]. Therefore, this calls for a pressing demand to efficiently enhance the solubility of drug. Many strategies have been devised by members of the scientific community to address this difficulty, the most prevalent of which is the production of amorphous solid dispersions (ASDs). ASD can be characterized as molecular distribution of an active ingredient in an amorphous carrier [4,5]. This process is ought to induce drug transition to amorphous structure making it more soluble in water. Both binary and ternary solid dispersions have been documented to enhance the solubility of insoluble drugs. However, an amorphous drug might revert to crystal structure with time or upon dissolution thereby reducing solubility. Therefore, an ASD system must meet rigorous standards for it to be considered successful, as it is important for the produced system to improve drug solubility while also stabilizing the amorphous molecule.

It is suggested that incorporating an additional polymer to an already existing binary system might alleviate these shortcomings. A number of studies have also demonstrated that ternary ASD are far more efficient than binary ASD in terms of enhancing solubility, stability and bioavailability [6] however polymers with different physicochemical attributes could affect the performance of the ternary ASD, thereby determining the best polymer remains critical [7]. Multiple studies had been carried out in the past years to demonstrate the efficacy of the binary SD approach in enhancing the solubility of curcumin. Our earlier work to improve aqueous solubility of curcumin also employed a binary ASD approach, wherein various binary dispersions of curcumin were prepared using bovine serum albumin (BSA), Hydroxy propyl methyl cellulose (HPMC E5), Poly ethylene glycol (PEG 6000) and Poly vinyl pyrolidine (PVP K30). Two different techniques namely kneading (KN) and solvent evaporation (S.E) were used to formulate dispersions and it was found that CUR: HPMC E5 (1:4 SE) and CUR: PVP K30 (1:4 kN) exhibited notable improvement in solubility and dissolution. In comparison, CUR: HPMC E5 (1:4 SE) presented highest solubility and thus was selected for the current investigation [8].

The current study is intended to formulate Ternary ASD of curcumin to further examine the possibilities of increasing curcumin's solubility and dissolving performance. Polymers chosen for this study are Soluplus®, Syloid® XDP 3150, Syloid® 244 and Poloxamer® 188. Soluplus® is a biocompatible polymer with exceptional solubilizing characteristics. In contrast to traditional solubilizers, it has dual functional properties such as an active solubilizer as well as matrix-forming polymer [9,10]. Based on a theoretical standpoint, it is an intriguing material to be employed as a vehicle as it is polar, non-ionic and its solubility remains constant throughout the alimentary system. Furthermore, it has somewhat surface activity too which may be beneficial to sustain overall super saturation [11, 12]. Incorporating drugs molecules within mesoporous silica has recently been deemed an interesting choice in solid dispersion development as nanosized mesopores can not only encapsulate API effectively but also prevent recrystallization [13,14]. Poloxamer 188® is poly (oxy) (ethylene) poly (propylene) co-block polymer. Multiple studies have reported their ability to superiorly enhance solubility in comparison to other polymers including cyclodextrins and poly ethylene glycols. They also present oral safety, surface activity and low melting temperature [15,16]. Even though some of these polymers have already been employed independently as binary carriers in enhancing the solubility of curcumin [17,18] however, the novelty of our work lies in evaluating the effect of these polymers as ternary carriers in enhancing the solubility of curcumin. To the best of our knowing, no prior work has been carried out regarding physicochemical evaluation and biological effectiveness of these polymers as ternary carriers in combination with HPMC-E5.

Therefore, the purpose of the current work was to demonstrate the impact of various ternary carriers (Soluplus®, Syloid® XDP 3150, Syloid® 244 and Poloxamer® 188) on the solubility, dissolution and biological activity of curcumin. In order to find a suitable polymer, twelve different ternary solid dispersions were formulated using solvent evaporation method. Different characterization studies were performed to determine the physicochemical properties of prepared ternary solid dispersions. Optimized formulations were also investigated for various biological activities including anti-bacterial, anti-oxidant and anti-inflammatory activity.

## 2. Materials and methods

### 2.1. Materials

Curcumin was obtained from Natural remedies private limited, Bangalore, India. Soluplus® was kindly gifted by BASF, Ludwigshafen, Germany. Syloid® XDP 3150 and Syloid® 244 were procured from Grace Davison discovery sciences, New Jersey, USA. Poloxamer® 188 was purchased from Sigma Aldrich, St. Louis, USA. Chemicals were employed as received.

### 2.2. Preparation of solid dispersions

Solid dispersions were formulated using solvent evaporation method [19] in which both polymer and drug are solubilized in a (volatile) solvent followed by evaporation of solvent. For ternary systems, each polymer was incorporated to the selected binary solid dispersion of curcumin at varied fraction of the total dry weight of binary dispersion (Table 1). The prepared mixture was then thoroughly dissolved in ethanol-water mixture (1:1) for duration of 15 min over a heated surface employing a magnetic stirrer. Added solvent was then removed by rotary evaporation followed by hot air oven to completely dehydrate the prepared dispersions. The completely dried dispersions were then crushed, sieved and preserved until further application.

### 2.3. Solubility study

Solubility of drug or solid dispersions was evaluated by adding an ample amount of CUR/ternary solid dispersion in a falcon tube consisting of distilled water. Afterwards addition each sample was vortex mixed for 3 min approximately and placed in a shaking water bath for two days. The resulting supernatant was then passed via a 0.45-μm membrane filter and subjected to spectrophotometric analysis (UV-1700, Shimadzu, Japan) at 370 nm [20].

### 2.4. Solid state characterization

#### 2.4.1. Fourier transforms infrared spectroscopy (FT-IR)

IR spectrum of drug and prepared solid dispersion was obtained employing Potassium bromide KBr disc method (Bruker T II, Germany) wherein each sample was scanned at a spatial resolution of 2 cm that varied from 4000 to 400 cm.

#### 2.4.2. X-ray diffraction (X-RD)

The diffraction data of the cur and selected SD formulations was determined using an X-ray diffractometer (Bruker D8, Germany) and each sample was analyzed across a grid of five to eighty degrees at a speed of 5° per minute.

#### 2.4.3. Scanning electron microscopy (SEM)

Surface characteristics of curcumin and selected SD formulations were studied by SEM (JSM-6480, Japan). A light covering of gold was sprayed over each formulation prior examination as a means to improve electrical conductivity.

#### 2.4.4. Differential scanning calorimetry (DSC)

Thermograms of curcumin and selected SD formulations were obtained through differential scanning calorimeter (Universal-V4.2E TA, USA). Each sample was placed in a closed aluminum pan and subjected to heat at an intensity of 10 °C per minute in the presence of nitrogen (20 mL/min) across a temperature spectrum ranging from 25 to 400 °C.

### 2.5. In-vitro dissolution

Dissolution testing was carried out by USP paddle apparatus II (PTWS 3CE, Pharma test, Germany). Pure curcumin and devised solid dispersions containing equivalent amount (10 mg) of curcumin were added to 900 mL of dissolution media (distilled water) maintained at 37°c temperature and 100 rpm speed. Samples (5 ml) from each formulation were collected at collected at specified intervals followed by filtration via a syringe filter and UV analysis (UV-1700, Shimadzu, Japan). Each sample was analyzed at 370 nm and sink conditions were maintained throughout the experiment [21].

**Table 1**
Composition of ternary solid dispersion formulations.

| Sr. no | Formulation code | Binary carrier | Drug: HPMC (W/W) | Ternary Carrier | Percentage of ternary polymer (W/W) |
|---|---|---|---|---|---|
| 1 | F1,F2,F3 | HPMC E5 | 1:4 | Soluplus® | 5 %,10 %, 20 % |
| 2 | F4,F5,F6 | HPMC E5 | 1:4 | Poloxamer 188® | 5 %,10 %, 20 % |
| 4 | F7,F8,F9 | HPMC E5 | 1:4 | Syloid® XDP | 5 %,10 %, 20 % |
| 4 | F10,F11,F12 | HPMC E5 | 1:4 | Syloid® 244 | 5 %,10 %, 20 % |

### 2.6. Biological characterization

#### 2.6.1. Antibacterial activity

Antibacterial activity of selected formulations was estimated using agar well diffusion assay following clinical and laboratory standards institute guidelines (CLSI 2015) [22,23]. For this, the nutrient-agar solution was formed and set to a 4-mm thick surface in glass petri dishes, successively followed by uniform distribution of 1 mL of $1.5 * 10^8$ Colony forming unit of each microbial suspension including *Bacillus cereus (B. Cereus), Escherichia coli* (*E. coli*), *Staphylococcus aureus (S. aureus)* and *Pseudomonas aeruginosa (P. aeruginosa)*. Thereafter wells of specified dimension (6 mm) were made in the agar material where 0.06 ml (40, 60, 80, 100 mg/ml in DMSO) of optimized formulations was placed. A strong antibiotic (ampicillin disks) was used as positive control and DMSO was employed negative control. Prepared agar plates were then incubated (37 °C, 24hrs) and the zone of inhibition was measured. All readings were recorded in triplicate. Minimum inhibitory concentrations (MIC) of selected formulations was also determined employing standard broth microdilution procedure following CLSI guidelines (CLSI 2015) [24] Serial dilutions of selected formulations were prepared by dissolving them in DMSO whereas the inoculums were accustomed to comprise about $1.5 \times 10^8$ colony forming unit per ml of tested bacteria. In order to estimate MIC 96 well microplate was employed and inoculum were added to each well in same amount as formulations. After the cycle was complete, plates were left at $36 \pm 1$ °C for a total of 24 h. Each plate was visually examined, and the lowest concentration without observable growth in every solid dispersion was determined to be the MIC.

#### 2.6.2. Antioxidant activity

Depending upon the radical scavenging activity of DPPH, Antioxidant activity of optimized formulation was determined by DPPH assay [25] where 2 mL of DPPH solution (0.1 Mm, Methanol) as control was incorporated to the optimized preparation (200 μl) subsequently followed by methanol addition (0.8 ml) and vigorous mixing was done by using vortex mixture (MX-S Vortex Mixer, Scilogex, USA). The container was then covered with aluminum foil and placed in a cool, dark place for 60 min to allow the reaction to occur. The reference standard was ascorbic acid. After 1.0 h incubation period, spectrophotometer (Cecil 7400-S, Cecil Instrumentation, Cambridge, England) was used to measure the absorbance of the samples at 517 nm. Experiment was repeated in triplicate to ensure accuracy and reproducibility. The scavenging activity of DPPH is calculated by using the given equation (1):

$$\% \text{ inhibition of DPPH} = [\text{Abs control} - \text{Abs sample} \ / \ \text{Abs control}] \times 100 \quad (1)$$

#### 2.6.3. Anti-inflammatory activity

Anti-inflammatory activity of optimized formulations was evaluated by a previously outlined method also known as bovine serum albumin denaturation method [26]. First of all different dilutions of each solid dispersions at definite concentrations (100, 250, 500 and 1000 μg per ml) were synthesized. Then 0.5 mL of these solutions was added 4.5 ml of bovine serum albumin (5 %) in order to prepare test solution. These test solutions were then incubated (37°c, 15 min) and positioned (60 °C, 60 min) in water subsequently. Obtained samples were then cooled at scanned at 660 nm using UV spectrophotometer. Degree of turbidity or denaturation was then calculated using following equation (2).

$$\text{Anti-inflammatory activity} = Yc - Ys \ / \ Yc \times 100 \quad (2)$$

Where, Yc = absorbance of control and Ys = Absorbance of sample.

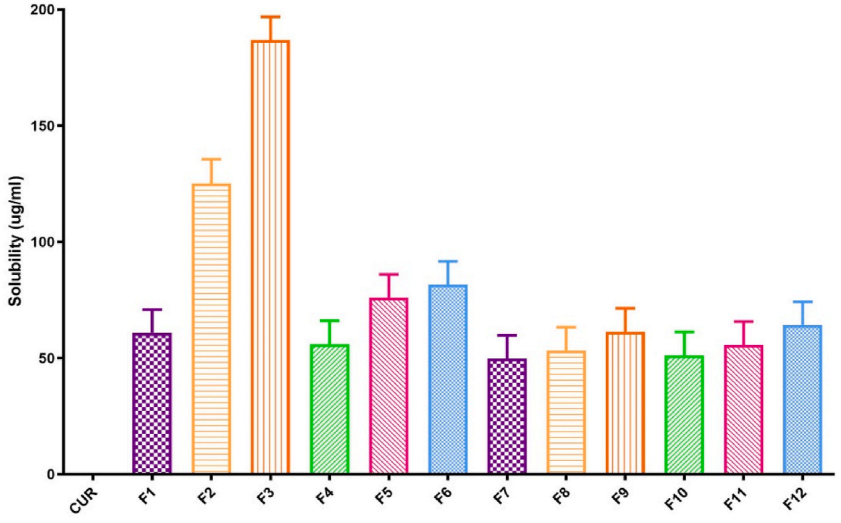


**Fig. 1.** Solubility measurements of pure curcumin (CUR) and prepared ternary solid dispersions (F1–F12). Error bars represents standard deviation (N = 3).

### 2.7. Statistical analysis

Statistical assessment was carried out by SPSS software version 20. All Quantitative figures were evaluated and presented as mean ± standard deviation.

## 3. Results and discussion

### 3.1. Solubility study

Curcumin is a highly hydrophobic drug with an aqueous solubility of 0.006 ± 2.40 μg/ml. Ternary Solid dispersions of curcumin were synthesized in order to investigate the impact of ternary carriers on the solubility of curcumin. Solubility measurements of curcumin (CUR) and prepared ternary solid dispersions (F1–F12) are displayed in Fig. 1. The incorporation of ternary carrier was found to significantly ($p < 0.05$) enhance the solubility of curcumin in comparison to pure drug. Furthermore, the solubility of curcumin was statistically enhanced when concentration of ternary carriers was increased from 5 % to 20 % w/w of dry weight of binary solid dispersion. Overall, the solubility value of curcumin was highest with Soluplus® followed by Poloxamer 188®, Syloid ® XDP 3150 and Syloid® 244.

Syloid® XDP 3150 and Syloid® 244 are highly porous and non-ordered mesoporous silica materials with surface area of 320 $m^2/g$ and 379 $m^2/g$ respectively. High surface area improves wettability and consequently solubility of the drug molecules [27,28]. The inclusion of Syloid® XDP 3150 and Syloid® 244 significantly enhanced the solubility of curcumin which was found to increase with increase in proportion of Syloid® XDP 3150 and Syloid® 244.Similar outcomes have been reported by other studies involving mesoporous silica where drugs were found to be in incomplete amorphasization i.e. precipitation of drug on the surface of the particles in crystal form at lower concentrations. The possible reason for this incomplete amorphasization was that the proportion of the drug was so high that only small amount of it was able to deposit within pores [29–31]. Depending upon the surface area formulations F10, F11 and F12 (containing Syloid® 244) displayed higher solubility rates in comparison to Formulation F7, F8 and F9 (containing Syloid ® XDP 3150). However this increment was comparably much smaller than Soluplus®. Poloxamer 188® exhibited improved solubility than Syloid® XDP 3150 and Syloid® 244.This could be ascribed to reduced surface tension and improved wetting characteristics of Polxamer 188® [32,33]. Furthermore incorporation of surfactants to solid dispersion formulation could also reduce super saturation and precipitation whilst enhancing drug solubility [34]. Increasing the concentration of Polxamer 188® from 5 to 20 percent (w/w) also significantly enhanced the solubility of curcumin. The improvement in solubility with escalating Poloxamer content suggests that Polxamer 188® possesses drug-solvent characteristics [35].

Among ternary carriers, maximum solubility was observed with soluplus, which was around 83 fold higher than pure curcumin. It can be seen that the results indicated considerable variance in solubility at different Soluplus® concentrations. An increase in concentration of soluplus® from 5 to 20 percent notably enhanced the solubility from 70.302 ± 5.32 μg/ml (F1) to 125.302 ± 4.87 μg/ml (F2) and 186.38 ± 3.95 μg/ml (F3). Maximum solubility was observed with F3. This increase in solubility can be explained by micellar solubilization characteristics of Soluplus® [36]. It has formerly been observed that soluplus® could reduce the nucleation process allowing the drug to remain supersaturated for an extended amount of time. Other possible reason could be glass transition (Tg) temperature of soluplus® (70°c) which helps in enhancing physical stability during storage [37]. Taken together soluplus® presented highest solubility with curcumin, therefore F1, F2 and F3 were chosen for further characterization.

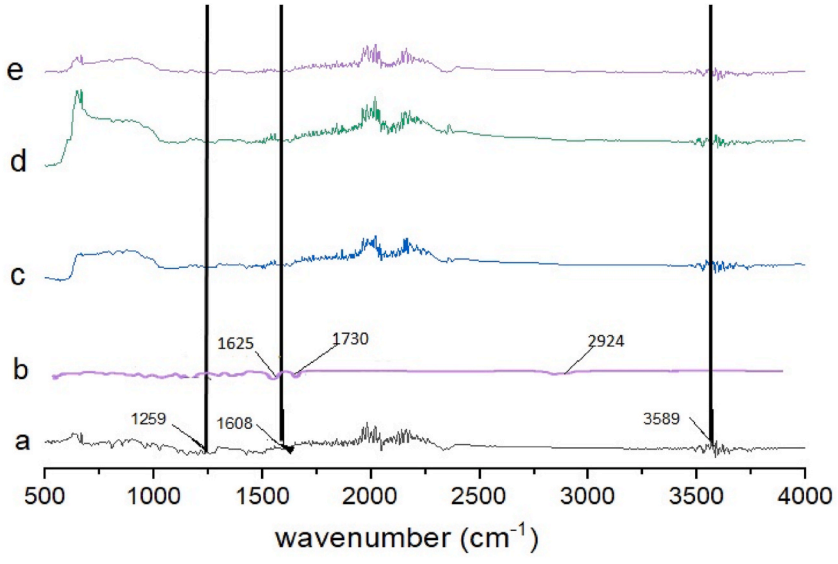


**Fig. 2.** Fourier transform IR spectra of (a) curcumin (CUR), (b) soluplus, and optimized solid dispersions of CUR with soluplus (c) F1, (d) F2, (e) F3.

### 3.2. Solid state characterization

#### 3.2.1. FTIR analysis

Fig. 2 show the infrared (IR) spectrum of Pure curcumin (CUR), pure Soluplus® (soluplus) and optimized solid dispersions of CUR with soluplus® (F1, F2,F3). FTIR absorption spectrum of CUR (Fig. 2a) was determined to be consistent with prior reports [38–40]. Main spectral bands of CUR were observed at 1259 (C–*O*–C stretching), 1608 (C═O Stretching) and 3589 (OH stretching) $cm^{-1}$.The IR spectrum of soluplus (2b) exhibited characteristic bands at 2924 (C–H stretching), 1632 and 1730 (C═O stretching) $cm^{-1}$. These results were parallel to the reported data of soluplus® [41–43]. The infrared spectrum of the prepared solid dispersion formulations F1 (Fig. 2c), F2 (Fig. 2d), F3 (Fig. 2e) readily demonstrated the characteristic bands of curcumin and soluplus confirming the existence of CUR and soluplus in all solid dispersion formulations. Furthermore no additional functional group was detected indicating there was no chemical reaction within curcumin. It was expected since the development of a solid dispersion had not been intended to yield something new, but rather to improve its physical and chemical characteristics.

#### 3.2.2. X-ray diffraction

XRD analysis of pure curcumin (CUR), pure Soluplus®, and optimized solid dispersions of CUR with soluplus (F1, F2 and F3) was performed in order to ascertain the physical features of curcumin in tailored dispersion formulation. Results of XRD are depicted in Fig. 3. CUR exhibited distinctive diffraction peaks starting from 7 to 27° which can be seen in Fig. 3a. Similar diffraction patterns have been reported by other studies which defended the presence of curcumin as crystal structure [44–46]. Soluplus presented no distinctive peaks which is suggestive of its amorphous nature (3b).The sharpness and intensity of these distinctive diffraction peaks of curcumin were found to reduce in solid dispersion formulations F1 (Fig. 3c), F2 (Fig. 3d), and F3 (Fig. 3e) further confirming the ability of employed carriers to successfully convert crystallized curcumin to amorphous form. Among solid dispersion formulations, F3 exhibited most reduction or even complete dissipation which was in agreement to its higher solubility and amorphousness.

#### 3.2.3. Scanning electron microscopy

SEM findings of pure curcumin (CUR), pure soluplus® (soluplus) and optimized Solid dispersion formulations (F1, F2, F3) are illustrated in Fig. 4.The microscopic study of CUR (Fig. 4a) presented flat, crooked shaped particles meanwhile soluplus (Fig. 4b) exhibited bulk masses with rough surface characteristics. Both of these SEM findings were in accordance with earlier reporting's of curcumin and soluplus® [47,48]. Conversely micrographs of optimized ternary solid dispersions (Fig. 4c, d, 4e) of curcumin exhibited bulky mass like structures with no trace of its aforementioned crooked shaped particles which confirmed uniform dispersion of curcumin throughout the ternary carrier and as well as its amorphous features. However despite being amorphous F1 and F2 (containing 5 and 10 % w/w soluplus®) produced somewhat coarser ternary solid dispersions which were completely amorphized in F3 (containing 20 % w/w soluplus®) indicating complete transition of curcumin to amorphous form and thereby higher solubility and dissolution.

#### 3.2.4. Differential scanning calorimetry (DSC)

DSC studies were carried out to determine phase changes of curcumin in solid dispersion formulations. Thermograms of pure Curcumin (CUR), pure soluplus® (soluplus) and optimized formulations (F1, F2, F3) are enlisted in Fig. 5. CUR (Fig. 5a) presented a sharp peak at 188 °C consistent to its melting temperature. DSC finding of curcumin were in agreement to its previous studies corroborating its crystal structure [49,50]. Soluplus showed a peak at 73.07 °C (Fig. 5b). The incidence of a shift or reduction in overall intensity of neat peaks is typically an indication of phase change towards amorphous state [51]. It was seen that the drug peak was

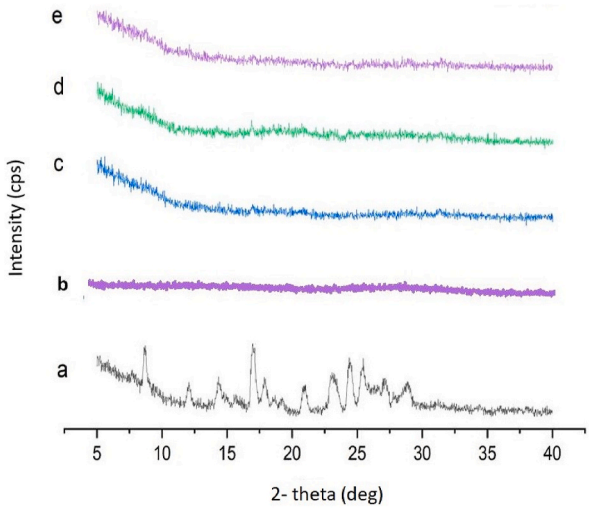


**Fig. 3.** Diffractograms of (a) curcumin (CUR), (b) soluplus and optimized solid dispersions of CUR with soluplus (c) F1, (d) F2, (e) F3.

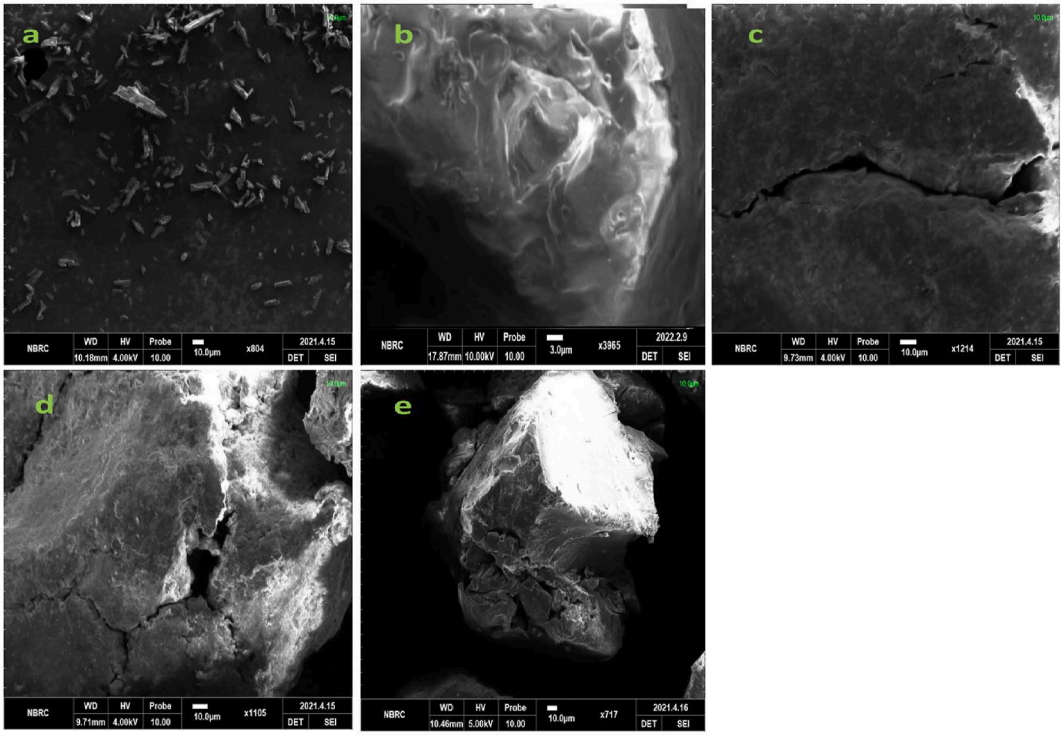


**Fig. 4.** SEM micrographs of (a) curcumin (CUR), (b) soluplus, and optimized solid dispersions of CUR with soluplus (c) F1, (d) F2, (e) F3.

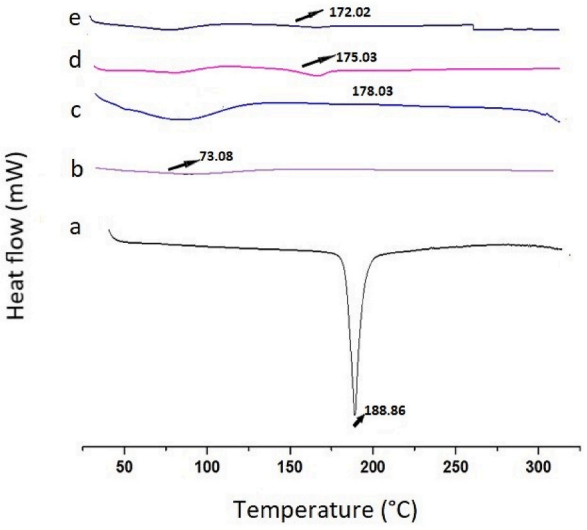


**Fig. 5.** Thermograms of (a) curcumin (CUR), (b) soluplus, and optimized solid dispersions of CUR with soluplus (c) F1, (d) F2, (e) F3.

shifted from 188.86 °C to 178.03 °C, 175.10 °C and 172.02 °C in the case of ternary solid dispersion F1 (Fig. 5c), F2 (Fig. 5d) and F3 (Fig. 5e) respectively. Furthermore, it was also observed that sharpness of peaks obtained with ternary solid dispersion formulations was also highly reduced. Overall, F3 exhibited the most disappearance of drug peaks verifying the aptitude of ternary carrier to entirely convert crystalline curcumin to amorphous phase (Fig. 5e).

### *3.2.5. In-vitro dissolution*

Physicochemical characteristics of drug particulates play an important role in drug dissolution. Drug release profile of pure curcumin and optimized solid dispersion formulations is presented in Fig. 6. Depending on data it can be articulated that incorporation of

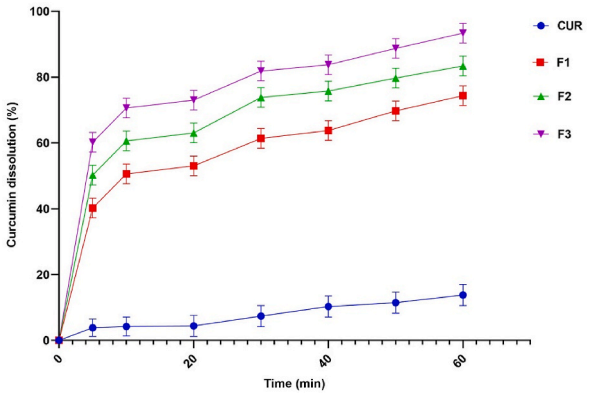


**Fig. 6.** Dissolution profile of CUR and optimized ternary solid dispersions (F, F2 and F3). Error bars represents standard deviation (N = 3).

ternary polymer soluplus® has notably enhanced the dissolution behavior of curcumin up to 91 % ± 3.89 in comparison to pure curcumin (10 % ± 2.58). Moreover as anticipated, formulation F3 (containing 20 % soluplus®) displayed highest drug dissolution which was in agreement with its solubility statistics. Similar findings were also reported by other researchers and it was identified that in comparison to other polymers soluplus® can significantly enhance drug solubility due to its amphiphillic structure [52,53]. Typically lipophilic vinyl acetate chains of soluplus® are involved in assuring the impregnation of polymer by outer surface of hydrophobic drug particles whilst the highly hydrophilic polyethylene glycol skeleton encompassing the drug particles extends steric hindrance which not only inhibits crystal growth but also cluster formation of drug particles thus creating optimal settings for enhanced drug dissolution [54,55]. Given that F3 presented highest dissolution with curcumin, therefore above this point only F3 was chosen for biological characterization.

### *3.3. Biological characterization*

#### *3.3.1. Antibacterial activity*

Antibacterial activity of CUR and F3 were examined against *S. aureus*, *B. cereus*, *P. aeruginosa* and *E. coli* strains. The efficacy of antibacterial activity of CUR and F3 was estimated by appraisal of zone of inhibition and Minimum inhibitory concentration (MIC). Findings of zone of inhibition and MIC are exhibited in Fig. 7 and Table 2 respectively. All bacteria were identified to be susceptive to solid dispersion formulation F3. CUR displayed smaller zone of inhibition (15 mm ± 2.15 for *S. aureus*, 14 mm ± 4.20 for *B. cereus*, 14 mm ± 2.12 for *E. -coli*, 14 mm ± 3.45 for *P. aeruginosa*) in comparison to F3 (24 mm ± 2.87 for *S. aureus*, 18 mm ± 2.63 for *B.cereus*, 18 mm ± 3.10 for *E. coli*, 18 mm ± 2.59 for *P. aeruginosa*) as mentioned in Fig. 7 A & B, which could be owed to the highly hydrophobic character of curcumin which might have hindered the leaching of drug in agar media [56]. MIC values of CUR were found to be significantly higher than F3 which was analogous to it solubility findings. Overall, we witnessed higher antibacterial activity against *S. aureus* with zone of inhibition of 24 mm ± 2.87 and MIC value of 135 μg/ml ± 5.9. The variation in antibacterial capabilities of F3 could be caused by presence of outer membrane in gram negative bacteria which hinders the introduction of antibiotics inside the bacterium and confers higher resilience to antibiotics [57]. As shown by numbers, F3 displayed improved antibacterial properties towards both Gram-positive and Gram-negative bacteria when compared to pure CUR. These findings were consistent with the previous research [58–60]. Given that both CUR and F3 were tested at exact same quantities of CUR greater antibacterial efficiency may be credited to superior water solubility and increased penetration potential of solid dispersion formulations in bacterium cell walls [61,62]. In short, F3 may be more appropriate for delivering curcumin to bacteria and hence maintains good antibacterial performance.

#### *3.3.2. Antioxidant activity*

Antioxidant activity of prepared solid dispersion formulation was assessed by employing DPPH as a standard free radical which in the presence of an antioxidant compound will be scavenged or inhibited [63,64]. Percentage inhibition activity of drug and optimized solid dispersion formulations is displayed in Fig. 8 which clearly exhibited that both CUR and solid dispersion formulation F3 presented notable scavenging activity with succession of activity as standard (96 % ± 4.80) > F3 (93 % ± 5.30) > CUR (69 % ± 4.79). Standard refers to ascorbic acid, which is a strong anti-oxidant and used as a positive control in this experiment for comparison to CUR and F3. Curcumin is widely recognized for its antioxidant effects which can be attributed to the presence of phenolic groups in its structural makeup however poor solubility of curcumin decreases its propensity to engage or scavenge free radicals [65]. An increase in solubility of curcumin in solid dispersion formulation has thereby enhanced its antioxidant potential [66,67].

#### *3.3.3. Anti-inflammatory studies*

In vitro anti-inflammatory potential of pure CUR and F3 was examined by analyzing the ability of tested formulations to denature BSA (Protein). Aspirin being strong anti-inflammatory agent was used as reference Standard (Positive control). In evident inflammatory ailments protein denaturation directs auto antigen production [68,69]. Substances than can avoid this phenomenon would

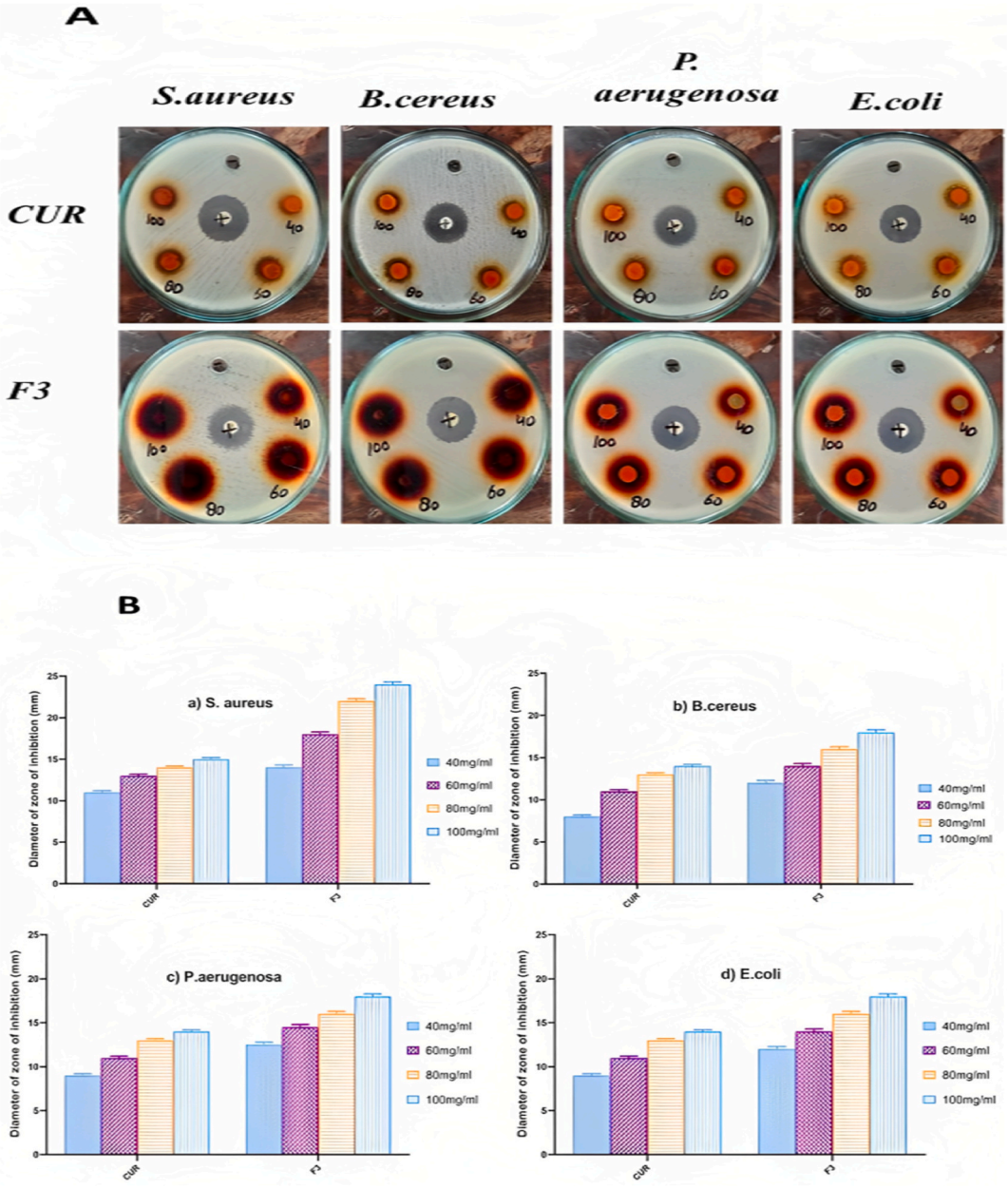


**Fig. 7.** Antibacterial activity of CUR and F3. (A) Photographs of diameter of zone of inhibition. (B) Graphical representation of diameter of zone of inhibition. Error bars represents standard deviation (N = 3).

**Table 2**
MIC of CUR and F3. Error bars represents standard deviation (N = 3).

| Code | MIC Values (μg/ml) | | | |
|---|---|---|---|---|
| | *S. aureus* | *B.cereus* | *P.aerugenosa* | *E.coli* |
| **CUR** | 219 ± 1.80 | 217 ± 3.50 | 175 ± 2.56 | 163 ± 3.10 |
| **F3** | 139 ± 2.79 | 157 ± 3.22 | 135 ± 2.50 | 123 ± 2.89 |

MIC = Minimum inhibitory concentration, CUR = Pure drug, *S. aureus* = *Staphylococcus aureus*, *B.cereus* = *Bacillus cereus*, *P.aeruginosa* = *Pseudomonas aeruginosa*, *E.coli* = *Escherichia coli*.

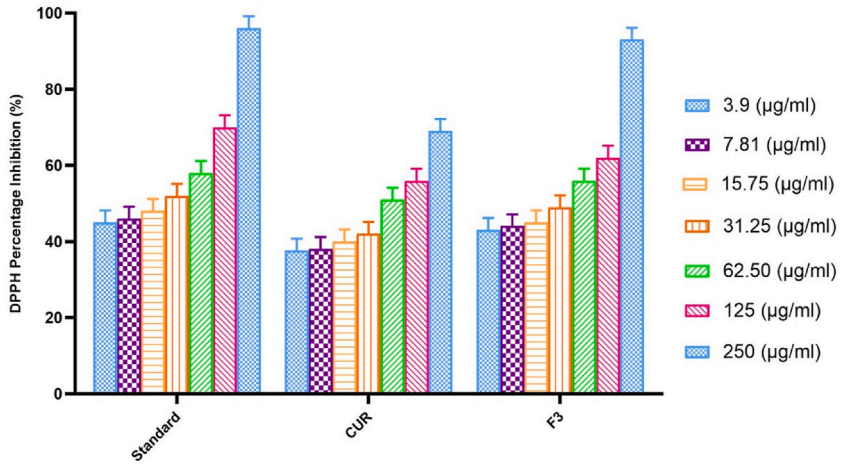


**Fig. 8.** Percent DPPH inhibition of CUR and F3. Error bars represents standard deviation (N = 3). Standard refers to Ascorbic acid, which is a strong anti-oxidant and used as a positive control for comparison to CUR and F3.

therefore be imperative for inflammation treatment Pure CUR and F3 significantly protected BSA from denaturation and increase in concentration of curcumin enhanced the inhibition potential correspondingly (Fig. 9). Largely F3 exhibited higher percent inhibition (80 % ± 3.16) in comparison to CUR (49 % ± 2.91) which was in agreement with its solubility data. Similar findings were reported by other investigations which presumed that solid dispersion formulations with improved solubility caused the drug to become more bioavailable thereby resulting in superior anti-inflammatory achievement [70,71].

### *3.4. Conclusion*

Ternary ASDs of curcumin using different ternary carriers (Soluplus®, Syloid® XDP 3150, Syloid® 244 and Poloxamer®) in combination with HPMC E5 (as binary carrier) were successfully formulated. The incorporation of ternary carriers was found to significantly ($p < 0.05$) enhance the solubility of curcumin in comparison to pure drug. Overall, the solubility value of curcumin was highest with Soluplus®. Increasing the concentration of Soluplus® from 5 % to 20 % (w/w of dry weight of binary solid dispersion) significantly increased curcumin's solubility and dissolving performance. Solid-state characterization also substantiated the formation of ASDs indicating complete transition of crystalline curcumin to amorphous form at 20 % w/w soluplus (F3). Biological testing of F3 also exhibited superior anti-bacterial, anti-oxidant and anti-inflammatory activities in comparison to pure curcumin suggesting F3 to be an effective vehicle in delivering curcumin.

## Ethics declaration

Review and/or approval by an ethics committee as well as informed consent was not required for this study because this study only used existing in-vitro studies and did not involve any direct experimentation/studies on living beings.

## Data availability statement

The data generated for this study is included in article.

## CRediT authorship contribution statement

**Memoona Ishtiaq:** Writing – original draft, Validation, Resources, Methodology, Investigation, Formal analysis. **Hina Manzoor:** Software, Resources, Investigation, Data curation. **Ikram Ullah Khan:** Resources, Methodology, Data curation. **Sajid Asghar:** Resources, Methodology, Data curation. **Muhammad Irfan:** Software, Resources, Formal analysis. **Norah A. Albekairi:** Resources, Funding acquisition. **Abdulrahman Alshammari:** Resources, Funding acquisition. **Abdulrahman F. Alqahtani:** Resources, Funding acquisition. **Saad Alotaibi:** Resources, Funding acquisition, Formal analysis. **Rabia Munir:** Validation, Resources, Investigation, Formal analysis. **Pervaiz A. Shah:** Software, Resources, Formal analysis. **Liaqat Hussain:** Resources, Formal analysis. **Muhammad Abubakar Saleem:** Software, Methodology. **Fizza Abdul Razzaq:** Validation, Resources, Investigation, Formal analysis. **Syed Haroon Khalid:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

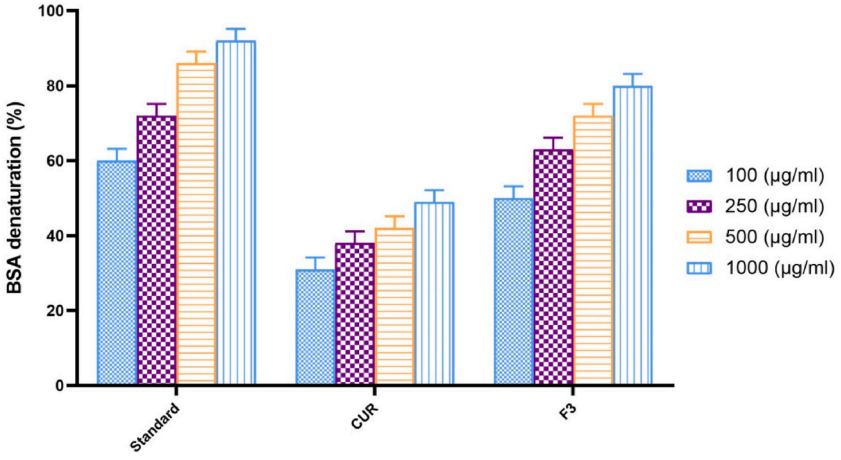


**Fig. 9.** Percent BSA denaturation of CUR and F3. Error bars represents standard deviation (N = 3). Standard refers to aspirin, which is a strong anti-inflammatory agent and used as a positive control for comparison to CUR and F3.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgments

Authors are thankful to the Researchers Supporting Project number (RSPD2024R1035), King Saud University, Riyadh, Saudi Arabia.

## References

[1] F. Fallahi, et al., Curcumin and inflammatory bowel diseases: from in vitro studies to clinical trials, Mol. Immunol. 130 (2021) 20–30.
[2] M. Pulido-Moran, et al., Curcumin and health, Molecules 21 (3) (2016) 264.
[3] S. Prasad, et al., Metal–curcumin complexes in therapeutics: an approach to enhance pharmacological effects of curcumin, Int. J. Mol. Sci. 22 (13) (2021) 7094.
[4] B. Zheng, D.J. McClements, Formulation of more efficacious curcumin delivery systems using colloid science: enhanced solubility, stability, and bioavailability, Molecules 25 (12) (2020) 2791.
[5] R.J. Chokshi, et al., Improving the dissolution rate of poorly water soluble drug by solid dispersion and solid solution—pros and cons, Drug Deliv. 14 (1) (2007) 33–45.
[6] Y. Huang, W.-G. Dai, Fundamental aspects of solid dispersion technology for poorly soluble drugs, Acta Pharm. Sin. B 4 (1) (2014) 18–25.
[7] Y. Lu, et al., Understanding the relationship between wettability and dissolution of solid dispersion, Int. J. Pharm. 465 (1–2) (2014) 25–31.
[8] M. Ishtiaq, et al., Development of the amorphous solid dispersion of curcumin: a Rational selection of polymers for enhanced solubility and dissolution, Crystals 12 (11) (2022) 1606.
[9] S.M. Alshahrani, et al., Stability-enhanced hot-melt extruded amorphous solid dispersions via combinations of Soluplus® and HPMCAS-HF, AAPS PharmSciTech 16 (2015) 824–834.
[10] A. Homayouni, et al., Promising dissolution enhancement effect of soluplus on crystallized celecoxib obtained through antisolvent precipitation and high pressure homogenization techniques, Colloids Surf. B Biointerfaces 122 (2014) 591–600.
[11] J. Lu, et al., Solid-state characterization of Felodipine–Soluplus amorphous solid dispersions, Drug Dev. Ind. Pharm. 42 (3) (2016) 485–496.
[12] A. Singh, et al., Effect of compression on the molecular arrangement of itraconazole–soluplus solid dispersions: induction of liquid crystals or exacerbation of phase separation? Mol. Pharm. 13 (6) (2016) 1879–1893.
[13] Y. He, et al., Mesoporous silica nanoparticles as potential carriers for enhanced drug solubility of paclitaxel, Mater. Sci. Eng. C 78 (2017) 12–17.
[14] M. Hanada, et al., Ternary amorphous solid dispersions containing a high-viscosity polymer and mesoporous silica enhance dissolution performance, Mol. Pharm. 18 (1) (2020) 198–213.
[15] A. Homayouni, et al., Preparation and characterization of celecoxib solid dispersions; comparison of poloxamer-188 and PVP-K30 as carriers, Iranian journal of basic medical sciences 17 (5) (2014) 322.
[16] H. Annepogu, H.A. Ahad, D. Nayakanti, Determining the best poloxamer carrier for thiocolchicoside solid dispersions, Turkish Journal of Pharmaceutical Sciences 17 (4) (2020) 372.
[17] H.Y. Aati, et al., Chemical composition and antimicrobial activity of the essential oils of Artemisia absinthium, Artemisia scoparia, and Artemisia sieberi grown in Saudi Arabia, Arab. J. Chem. 13 (11) (2020) 8209–8217.
[18] M. Vukićević, et al., Poloxamer-based curcumin solid dispersions for ex tempore preparation of supersaturated solutions intended for antimicrobial photodynamic therapy, Pharmaceut. Dev. Technol. 20 (7) (2015) 863–871.
[19] J.X. Wu, et al., Influence of solvent evaporation rate and formulation factors on solid dispersion physical stability, Eur. J. Pharmaceut. Sci. 44 (5) (2011) 610–620.
[20] G.O.K. Loh, Y.T.F. Tan, K.-K. Peh, Enhancement of norfloxacin solubility via inclusion complexation with β-cyclodextrin and its derivative hydroxypropyl-β-cyclodextrin, Asian J. Pharm. Sci. 11 (4) (2016) 536–546.
[21] S. Khan, et al., Physicochemical characterisation, drug polymer dissolution and in vitro evaluation of phenacetin and phenylbutazone solid dispersions with polyethylene glycol 8000, J. Pharmaceut. Sci. 100 (10) (2011) 4281–4294.
[22] W.L. Clsi, M02-A11: performance standards for antimicrobial disk susceptibility tests; Approved Standard, CLSI Clin. Laboratory Stand. Inst 32 (1) (2015).
[23] J.H. Jorgensen, M.J. Ferraro, Antimicrobial susceptibility testing: general principles and contemporary practices, Clin. Infect. Dis. (1998) 973–980.

[24] G. Yurtdaş-Kırımlıoğlu, Development and characterization of lyophilized cefpodoxime proxetil-Pluronic® F127/polyvinylpyrrolidone K30 solid dispersions with improved dissolution and enhanced antibacterial activity, Pharmaceut. Dev. Technol. 26 (4) (2021) 476–489.
[25] K. Sirivibulkovit, S. Nouanthavong, Y. Sameenoi, Based DPPH assay for antioxidant activity analysis, Anal. Sci. 34 (7) (2018) 795–800.
[26] Y.A. Bailey-Shaw, et al., In-vitro evaluation of the anti-inflammatory potential of selected jamaican plant extracts using the bovine serum albumin protein denaturation assay, Int. J. Pharmaceut. Sci. Rev. Res. 47 (1) (2017) 145–153.
[27] K.K. Qian, R.H. Bogner, Application of mesoporous silicon dioxide and silicate in oral amorphous drug delivery systems, J. Pharmaceut. Sci. 101 (2) (2012) 444–463.
[28] O. Planinšek, B. Kovačič, F. Vrečer, Carvedilol dissolution improvement by preparation of solid dispersions with porous silica, Int. J. Pharm. 406 (1–2) (2011) 41–48.
[29] Z. Wang, et al., Exploring the potential of mesoporous silica as a carrier for puerarin: characterization, physical stability, and in vivo pharmacokinetics, AAPS PharmSciTech 20 (2019) 1–12.
[30] T.-T. Le, et al., Delivery of poorly soluble drugs via mesoporous silica: impact of drug overloading on release and thermal profiles, Pharmaceutics 11 (6) (2019) 269.
[31] H.-m. Yan, et al., Improvement in oral bioavailability and dissolution of tanshinone IIA by preparation of solid dispersions with porous silica, J. Pharm. Pharmacol. 67 (9) (2015) 1207–1214.
[32] Š. Zupančič, et al., Effects of electrospinning on the viability of ten species of lactic acid bacteria in poly (ethylene oxide) nanofibers, Pharmaceutics 11 (9) (2019) 483.
[33] F. Yan, et al., The effect of poloxamer 188 on nanoparticle morphology, size, cancer cell uptake, and cytotoxicity, Nanomed. Nanotechnol. Biol. Med. 6 (1) (2010) 170–178.
[34] C.E. Correa-Soto, et al., Role of surfactants in improving release from higher drug loading amorphous solid dispersions, Int. J. Pharm. 625 (2022) 122120.
[35] S. Chutimaworapan, et al., Effect of water-soluble carriers on dissolution characteristics of nifedipine solid dispersions, Drug Dev. Ind. Pharm. 26 (11) (2000) 1141–1150.
[36] R. Pignatello, R. Corsaro, Polymeric nanomicelles of Soluplus® as a strategy for enhancing the solubility, bioavailability and efficacy of poorly soluble active compounds, Current Nanomedicine (Formerly: Recent Pat. Nanomed. 9 (3) (2019) 184–197.
[37] M. Rahman, et al., Spray-dried amorphous solid dispersions of griseofulvin in HPC/soluplus/SDS: elucidating the multifaceted impact of SDS as a minor component, Pharmaceutics 12 (3) (2020) 197.
[38] A. Rohman, D. Ramadhani, A. Nugroho, Analysis of curcumin in Curcuma longa and Curcuma xanthorriza using FTIR spectroscopy and chemometrics, Res. J. Med. Plant 9 (4) (2015) 179–186.
[39] S. Darandale, P. Vavia, Cyclodextrin-based nanosponges of curcumin: formulation and physicochemical characterization, J. Inclusion Phenom. Macrocycl. Chem. 75 (2013) 315–322.
[40] H. Lestari, et al., Simultaneous analysis of Curcumin and demethoxycurcumin in Curcuma xanthorriza using FTIR spectroscopy and chemometrics, Int. Food Res. J. 24 (5) (2017).
[41] J. Djuris, et al., Preparation of carbamazepine–Soluplus® solid dispersions by hot-melt extrusion, and prediction of drug–polymer miscibility by thermodynamic model fitting, Eur. J. Pharm. Biopharm. 84 (1) (2013) 228–237.
[42] Y. Lan, S. Ali, N. Langley, Characterization of Soluplus by FTIR and Raman Spectroscopy, BASF Corporation, Pharma Ingredients and Services, Tarrytown, NY, USA, 2010.
[43] S. Patnaik, et al., Aceclofenac-Soluplus® nanocomposites for increased bioavailability, Soft Nanosci. Lett. 5 (2) (2015) 13.
[44] J. Shaikh, et al., Nanoparticle encapsulation improves oral bioavailability of curcumin by at least 9-fold when compared to curcumin administered with piperine as absorption enhancer, Eur. J. Pharmaceut. Sci. 37 (3–4) (2009) 223–230.
[45] Y. Chen, et al., Preparation and blood compatibility of electrospun PLA/curcumin composite membranes, Fibers Polym. 13 (2012) 1254–1258.
[46] C. Arab, R. El Kurdi, D. Patra, Efficient removal of Congo red using curcumin conjugated zinc oxide nanoparticles as new adsorbent complex, Chemosphere 276 (2021) 130158.
[47] Y.-c. Zeng, et al., Soluplus micelles for improving the oral bioavailability of scopoletin and their hypouricemic effect in vivo, Acta Pharmacol. Sin. 38 (3) (2017) 424–433.
[48] F.S. Tabatabaei Mirakabad, et al., A Comparison between the cytotoxic effects of pure curcumin and curcumin-loaded PLGA-PEG nanoparticles on the MCF-7 human breast cancer cell line, Artif. Cell Nanomed. Biotechnol. 44 (1) (2016) 423–430.
[49] P. Jourghanian, et al., Sustained release curcumin loaded solid lipid nanoparticles, Adv. Pharmaceut. Bull. 6 (1) (2016) 17.
[50] D. Yadav, N. Kumar, Nanonization of curcumin by antisolvent precipitation: process development, characterization, freeze drying and stability performance, Int. J. Pharm. 477 (1–2) (2014) 564–577.
[51] G. Rüzgar, et al., Studies on improvement of water-solubility of curcumin with electrospun nanofibers, Fabad J. Pharm. Sci. 38 (3) (2013) 143.
[52] B.R. Giri, et al., Hot-melt extruded amorphous solid dispersion for solubility, stability, and bioavailability enhancement of telmisartan, Pharmaceuticals 14 (1) (2021) 73.
[53] X. Ma, et al., Influence of carbamazepine dihydrate on the preparation of amorphous solid dispersions by hot melt extrusion, Pharmaceutics 12 (4) (2020) 379.
[54] J. Guan, et al., Synergetic effect of nucleation and crystal growth inhibitor on in vitro-in vivo performance of supersaturable lacidipine solid dispersion, Int. J. Pharm. 566 (2019) 594–603.
[55] H. Yang, et al., Investigation of a nanosuspension stabilized by Soluplus® to improve bioavailability, Int. J. Pharm. 477 (1–2) (2014) 88–95.
[56] M. Tummalapalli, et al., Composite wound dressings of pectin and gelatin with aloe vera and curcumin as bioactive agents, Int. J. Biol. Macromol. 82 (2016) 104–113.
[57] S. Asghar, et al., Plant-derived nanotherapeutic systems to counter the overgrowing threat of resistant microbes and biofilms, Adv. Drug Deliv. Rev. 179 (2021) 114019.
[58] A. Kassem, et al., Antimicrobial activity of chloramphenicol in solid dispersion systems, Pharmazie 34 (1) (1979) 43–44.
[59] T.F. Alves, et al., Association of silver nanoparticles and curcumin solid dispersion: antimicrobial and antioxidant properties, AAPS PharmSciTech 19 (2018) 225–231.
[60] L. Fitriani, et al., Hydrogel formulation of usnic acid and antibacterial activity test against propionibacterium acne, Sci. Pharm. 87 (1) (2019) 1.
[61] J. Ghaderkhani, et al., Improved antibacterial function of Rifampicin-loaded solid lipid nanoparticles on Brucella abortus, Artif. Cell Nanomed. Biotechnol. 47 (1) (2019) 1181–1193.
[62] E. Gundogdu, C. Koksal, E. Karasulu, Comparison of cefpodoxime proxetil release and antimicrobial activity from tablet formulations: complexation with hydroxypropyl-β-cyclodextrin in the presence of water soluble polymer, Drug Dev. Ind. Pharm. 38 (6) (2012) 689–696.
[63] F. Shahidi, Y. Zhong, Measurement of antioxidant activity, J. Funct.Foods 18 (2015) 757–781.
[64] C.I. Tuberoso, et al., Determination of antioxidant compounds and antioxidant activity in commercial oilseeds for food use, Food Chem. 103 (4) (2007) 1494–1501.
[65] J.S. Wright, Predicting the antioxidant activity of curcumin and curcuminoids, J. Mol. Struct.: THEOCHEM 591 (1–3) (2002) 207–217.
[66] S. Alshehri, et al., Enhanced dissolution of luteolin by solid dispersion prepared by different methods: physicochemical characterization and antioxidant activity, ACS Omega 5 (12) (2020) 6461–6471.
[67] A.R. de Mello Costa, et al., Quercetin-PVP K25 solid dispersions: preparation, thermal characterization and antioxidant activity, J. Therm. Anal. Calorim. 104 (1) (2011) 273–278.
[68] A. Azeem, et al., Anti–inflammatory activity of the glandular extracts of Thunnus alalunga, Asian Pac. J. Tropical Med. 3 (10) (2010) 794–796.

[69] N.P. Nirmal, P. Panichayupakaranant, Antioxidant, antibacterial, and anti-inflammatory activities of standardized brazilin-rich Caesalpinia sappan extract, Pharmaceut. Biol. 53 (9) (2015) 1339–1343.
[70] K.C. Ofokansi, et al., Improved dissolution and anti-inflammatory activity of ibuprofen-polyethylene glycol 8000 solid dispersion systems, International journal of pharmaceutical investigation 6 (3) (2016) 139.
[71] M. Jafar, D. Mhg, A. Shareef, Enhancement of dissolution and anti-inflammatory effect of meloxicam using solid dispersions, Int. J. Appl. Pharm. 2 (1) (2010) 22–27.